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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/555,270 | 08/30/2000 | Catharina Svanborg | 032313-003 | 4240 |

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| EXAMINER |
|---|
| HOLLERAN, ANNE L |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | 21 |

DATE MAILED: 05/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/555,270 | SVANBORG, CATHARINA | |
| | Examiner | Art Unit | |
| | Anne Holleran | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *24-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *49-52* is/are allowed.

6)☒ Claim(s) *24-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. The amendment filed February 6, 2003 (Paper No. 20) is acknowledged. Claims 1-5 and 11-23 were canceled.

2. Claims 24-52 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The declaration of Dr. Svanborg has been considered.

***Objections and Rejections Withdrawn:***

5. The rejection of claims 1, 11-13 under 35 U.S.C. 102(b) as being anticipated by Sabharwal et al (WO 96/04920; published 22 February 1996; cited in IDS) as evidenced by Kuwajima (Kuwajima, K., FASEB Journal, 10: 102-109, 1996; cited in IDS) is withdrawn in view of the declaration and in view of the cancellation of claims.

6. The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Hakansson et al (Hakansson, A. et al, Proc. Natl. Acad. Sci., USA, 92: 8064-8068, 1995; cited in IDS) as evidenced by Kuwajima (Kuwajima, K., FASEB Journal, 10: 102-109, 1996; cited in IDS) is withdrawn in view of the declaration and in view of the cancellation of the claims.

7. The rejection of claims 1-5, 11-14 and 20-23 under 35 U.S.C. 112, first paragraph, for lack of enablement, is withdrawn in view of the amendment canceling the claims. In view of applicant's persuasive arguments, the same grounds of rejection are not applied to the new claims.

***New Grounds of Rejection:***

8. Claims 37-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that new claims 37-40 introduce new matter into the specification.

Claims 37-40 are drawn to complexes comprising MAL and a cytotoxin that is active in the nucleoplasm. The cytotoxin may be a microbial toxin, a chemotherapeutic agent or an antibody. The specification fails to provide support for the subgenus of cytotoxin that is active in the nucleoplasm. The specification teaches that MAL may be complexed with a further reagent that supplements the effect of MAL in killing tumor cells (page 3, lines 14-16). The specification also teaches that the further reagent may be chemotherapeutic reagent, a microbial toxin or a monoclonal antibody, but fails to teach that any of these agents are specifically active in the nucleoplasm. The specification also provides the example of a microbial toxin that is diptheria toxin, which appears to be a toxin that is active in the cytoplasm of cells (see U.S. Patent 6,455,673; col. 1, lines 16-42). The specification fails to characterize a genus of chemotherapeutic agent or antibody that is active in the nucleoplasm.

Because one of the examples of a further reagent is not one which is active in the nucleoplasm of cells, and because the specification also lacks *ipsis verbis* support for the genus of "cytotoxin that is active in the nucleoplasm", and further, because the specification fails to provide structurally representative members of the genus of "cytotoxin that is active in the nucleoplasm", the specification fails to provide written description of the genus of "cytotoxin that is active in the nucleoplasm", the subgenus of microbial toxin that is active in the nucleoplasm, the subgenus of chemotherapeutic agent that is active in the nucleoplasm, or the subgenus of antibody that is active in the nucleoplasm.

Applicant is reminded that the written description requirement of 35 U.S.C. 112, first paragraph is severable from the enablement requirement of 35 U.S.C. 112, first paragraph.

9. Claims 24, 26-30, 32, 34-39 and 41-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sabharwal et al (WO 96/04920; published 22 February 1996; cited in IDS) in view of Johnstone and Thorpe (Immunochemistry in Practice, Blackwell Scientific Publications, Oxford, 1987; pages 113-130) and also in view of Goers (Goers, J. Immunochemical Techniques Laboratory Manual, Academic Press, New York, 1993; pages 69-79).

The inventions of claims 24, 26-29, 32, 34-36 are drawn to methods of combining MAL with a reagent to form a complex and applying the reagent to cells. The reagent may be capable of killing cells, may be a diagnostic reagent, may be coupled by conjugation or covalent bonding, may be a cytotoxin, a chemotherapeutic agent, or a microbial toxin, may be a labeling agent, may be biotin or a radioactive label, or may be $^{125}I$, $^{14}C$, or $^{35}S$. The inventions of claims 37-39 and 41-47 are drawn to protein complexes comprising MAL and a cytotoxin, wherein the cytotoxin is

active in the nucleoplasm. The limitation of activity in the nucleoplasm does not restrict activity to the nucleoplasm. Because activity is not restricted to activity in the nucleoplasm, the claims read on a combination with label or radioactive moiety, which may also have the function of being toxic to microbes or be useful as a chemotherapetic agent. Claims 44-47 are drawn to pharmaceutical compositions, which are interpreted with the same scope as the products comprised within the pharmaceutical compositions, because the phrase "pharmaceutical composition" is interpreted as an intended use clause, which does not limit the claimed product.

Sabharwal teaches that MAL has antiadhesive properties in certain bacterial strains, and also is a bactericide for at least *S. Pneumoniae*. Sabharwal teaches pharmaceutical preparations, such as pharmaceutical preparations in a cream form, and teaches methods of applying MAL to cells. It would have been prima facie obvious to one of skill in the art at the time the invention was made to have combined MAL with a reagent useful in detection for the purpose of quantifying uptake of MAL in bacteria. An example of a reagent useful for detection purposes is a radiolabel or biotin. A radiolabel also happens to be a reagent that is capable of killing cells, and therefore, may also be a cytotoxin. Sabharwal fails to teach making complexes of MAL with any reagent. However, methods of labeling proteins with radioactive labels or biotin is well known in the art as evidenced by the teachings of Johnstone and Thorpe or of Goers. Johnstone and Thorpe teaches radiolabeling of proteins and demonstrates how to radiolabel with $^{125}I$, $^{14}C$, or $^{35}S$. Goers teaches labeling of antibodies and teaches how to label with biotin, and also how to couple biotin to a protein with a succinamidyl ester linking group.

10. Claims 24-30, 32-39, and 41-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hakansson et al (Hakansson, A. et al, Proc. Natl. Acad. Sci., USA, 92: 8064-8068, 1995; cited in IDS) in view of Johnstone and Thorpe (Immunochemistry in Practice, Blackwell Scientific Publications, Oxford, 1987; pages 113-130) and also in view of Goers (Goers, J. Immunochemical Techniques Laboratory Manual, Academic Press, New York, 1993; pages 69-79).

Hakaansen teaches that MAL causes apoptosis in tumor cells. Hakaanesen teaches applying MAL to cells. Therefore, it would have been prima facie obvious to one of skill in the art at the time the invention was made to have combined MAL with a reagent useful in detection for the purpose of quantifying uptake of MAL in tumor cells or for the determination of specificity of MAL uptake. An example of a reagent useful for detection purposes is a radiolabel or biotin. A radiolabel also happens to be a reagent that is capable of killing cells, and therefore, may also be a cytotoxin, a chemotherapeutic agent or a microbial toxin. Hakaansen fails to teach making complexes of MAL with any reagent. However, methods of labeling proteins with radioactive labels or biotin is well known in the art as evidenced by the teachings of Johnstone and Thorpe or of Goers. Johnstone and Thorpe teaches radiolabeling of proteins and demonstrates how to radiolabel with $^{125}I$, $^{14}C$, or $^{35}S$. Goers teaches labeling of antibodies and teaches how to label with biotin, and also how to couple biotin to a protein with a succinamidyl ester linking group.

11. Claims 24 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hakansson et al (Hakansson, A. et al, Proc. Natl. Acad. Sci., USA, 92: 8064-8068, 1995; cited in

IDS) or Sabharwal et al (WO 96/04920; published 22 February 1996; cited in IDS) in view of Robinett (Robinett, C.C. et al, Journal of Cell Biology, 135(6): 1685-1700, 1996).

Claims 24 and 31 are interpreted as drawn to methods comprising combining MAL with a reagent to form a complex, applying the complex to cells, wherein the reagent is polypeptide or protein fused to MAL. Hakansson teaches that MAL causes apoptosis in tumor cells, and teaches methods of applying MAL to cells. Sabharwal teaches that MAL has antiadhesive properties in certain bacterial strains, and also is a bactericide for at least *S. Pneumoniae*. Therefore, it would be obvious to make methods where MAL is complexed to a label for the purpose of detecting and quantifying uptake of MAL. The detection agent may be a protein such as green fluorescent protein, which is used in methods where the mode of detection is fluorescence microscopy. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have made a complex of MAL fused with a protein such as green fluorescent protein. Neither Hakansson nor Sabharwal teaches fusion of MAL with a protein such as green fluorescent protein. However, methods for making fusion proteins with green fluorescent protein are known in the art as evidenced by the teachings of Robinett (see page 1687, 2$^{nd}$ col.).

12. Claims 37-41, 44, 45 and 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hakansson et al (Hakansson, A. et al, Proc. Natl. Acad. Sci., USA, 92: 8064-8068, 1995; cited in IDS) in view of Mattes (U.S. Patent 5,759,514; issued June, 1998; effective filing date Apr., 1994).

Claims 37-41, 44, 45 and 48 are drawn to complexes comprising MAL and a cytotoxin or labeling agent, and to a method for treating cancer. The complex comprises MAL and cytotoxin that is active in the nucleoplasm of cells. The cytotoxin may be a microbial agent or a chemotherapeutic agent.

Hakansson teaches MAL, and teaches that MAL induces apoptosis in tumor cells and not in some non-cancerous cells. Thus, Hakansson teaches that MAL may be used as tumor targeting agent. Hakansson fails to teach MAL as part of a complex, and fails to teach therapeutic methods. However, Mattes teaches therapeutic methods comprising administerting a tumor targeting protein or polypeptide conjugated to a nucleic acid-targeting small molecule labeled with an Auger electron-emitting radionuclide (such as $^{125}I$). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a complex of MAL with a nucleic acid-targeting small molecule labeled with a radionuclide such as $^{125}I$, because the prior art teaches that MAL exhibits some specificity to tumor cells.

13. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hakansson et al (Hakansson, A. et al, Proc. Natl. Acad. Sci., USA, 92: 8064-8068, 1995; cited in IDS) in view of Goldenberg (U.S. Patent 4,348,376; issued Sep. 1982).

Claim 48 is drawn to a method of treatment comprising administering to a patient in need of cancer treatment a complex of MAL and a cytotoxin that is active in the nucleus of a cell. Claim 48 reads on an in vivo diagnostic procedure, because the active steps comprise administering MAL and a cytotoxin, where the cytotoxin may include a radioactive label. A

radioactive label may be used in either a detection method or in a chemotherapeutic method. Applicant is reminded that the movtivation for combining teachings in the prior art does not have to be the same motivation as that taught by the specification.

Hakansson teaches that MAL causes apoptosis in cancer cells and appears to have some specificity for cancer cells. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have labeled MAL and administered it in vivo to detect which tissues take up MAL. Hakansson fails to teach labeling of MAL, and fails to teach administration to a patient. However, methods for in vivo administration of proteins and radiolabeling are known in the art as evidenced by the teachings of Goldenberg, which teaches general methods for labeling antibodies with radiolabels that are useful for in vivo detection of antibody uptake (col. 4, lines 10-52).

***Conclusion***

Claims 49-52 are free of the prior art, because they require the specific step of detecting label in the nucleus. The prior art does not teach or fairly suggest methods for the diagnosing of cancer comprising administering or applying a protein complex comprising MAL and a labeling agent and then the detection of the label in the nucleus. Claims 49-52 are allowable.

Claims 24-48 are rejected.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
April 25, 2003

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